
Editorial

The carcinogenic effect of exposure to low doses of carcinogens[★]

The aim of this paper is to discuss the validity of the assessment of the carcinogenic effect of exposure to low doses of carcinogens. This problem is of major importance both in the fields of occupational and environmental hazards. From the middle ages to the nineteenth century the common view, expressed by Paracelsius and Claude Bernard, was that "tout est poison, rien n'est poison, tout est question de dose" ("everything is toxic, nothing is toxic, toxicity is related to dose"). During this period most of the drugs were compounds that were toxic at high concentrations but had (or were supposed to have) a beneficial effect at low doses. Claude Bernard's statement was only recently challenged when the concept of a stochastic effect was introduced. Under this model, diseases such as cancer or teratogenic defects are caused by a mutation, or a genomic defect, in one somatic cell. Thus the probability of inducing a specific defect in one of the 60 000 billion cells of the human body is related to the dose. In this model the probability decreases as the dose lowers but never becomes equal to zero.

Low doses or concentrations are those that have no detectable carcinogenic effect in experimental animals. No reliable epidemiological data exist for low doses in humans; however, the absence of a significant increase in the incidence of cancer in the populations studied cannot exclude a carcinogenic effect so small as to be undetectable even in a population of tens of thousands of subjects.

Ionising radiations are a good example of such a situation. Since its birth the earth has been radioactive, cosmic rays have always irradiated our planet, and life has developed in a bath of ionising radiation. In France, the United Kingdom, and the United States the dose of natural irradiation varies from region to region and ranges from 1.5 to 6 millisievert (mSv) per year.¹ Epidemiological and experimental

data clearly show that acute irradiation at a dose equal to or greater than 400 mSv significantly increases the incidence of cancer. What is the risk associated with a low dose, for example 4 mSv delivered at a low dose rate? The risk could be equal to zero if a threshold exists and corresponds to a dose higher than 4.1 mSv. The risk is equal to one hundredth of the risk associated with a dose of 400 mSv if the dose effect relation is linear. The risk could be so small as to be negligible if the effect is related to the square (or a higher power) of the dose.²

The implications of these three models are different. Under the first and third models the health consequences of exposure to a low dose are small, whereas with the second they may be unacceptable. The regulation agencies have to define admissible exposure, in other words the level at which an exposure is safe. In health and environmental protection the common belief is that it is better to overestimate rather than underestimate the detrimental effect of an exposure. This view needs to be discussed and its consequences examined.

The carcinogenicity of low dose exposure has been the theme of very active debate for the past decade, and has been challenged in several articles. In a recent editorial Abelson, associate editor of the journal *Science*, wrote that "stringent regulation and frightening publicity have led to public anxiety and chemophobia . . . the cost of cleaning up phantom hazards will be in the hundreds of billions of dollars with minimal benefit to human health. In the meantime real hazards are not receiving adequate attention."³ If true, this means that the governments of industrialised countries are wasting vast amounts of money for a limited health benefit. One hundred billion dollars is such a huge amount of money that it is difficult to visualise, but that was the cost of the Marshall Plan to rebuild western Europe after the second world war. Many useful things could be done with several hundred billions of dollars; to waste this money on phantom hazards would be detrimental for society as the budget for health and environment is limited. In particular the amount of money that can be devoted to the fight against cancer is limited. The

[★]Based on the keynote speech delivered at the symposium: *Low dose exposure to natural and man made fibres: towards a collaborative European epidemiology*, Paris 10-12 June 1991. A report of the symposium appears in this journal, pp 606-614.

money available for prevention has to be shared between reduction of occupational exposure, epidemiological and experimental research, informing the public and workers, and regulation and control of public exposure. Moreover, we have to consider the indirect financial and social consequences of the prohibition of useful agents and the indirect cost of reducing concentrations of suspected chemicals. It can even be argued that too stringent regulation can be detrimental—for example, the ban on potent insecticides such as DDT has resulted in an increase in the incidence of malaria in India and south east Asia. It has been asserted that banning DDT without replacing it with inexpensive substitutes may have caused several tens of thousands of lethal cases of malaria. With regard to CFCs, their possible impact on the ozone layer in the polar regions has to be balanced against the benefits of an inexpensive technique of food refrigeration, which has been one of the most important factors in health improvement during the 20th century. We must remain vigilant and should not accept that an increase in the cost of refrigerators jeopardise their use in developing countries. Similarly, the overestimation of the detrimental effects of radioactivity has hampered the development of nuclear energy and favoured the use of coal and fuel, the combustion of which produces carcinogens and induces a greenhouse effect; thus fossil fuels may have detrimental effects on health far greater than those of nuclear energy. These examples show that overestimating the risks of a chemical or physical agent has consequences that ought to be taken into account. The realistic assessment of the carcinogenic effect of exposure to low doses is therefore of great practical, financial, and scientific importance.

The usual procedure in public health involves two steps: the first one is quantitatively to assess the carcinogenic effect at high doses, on the basis of epidemiological and experimental data mainly from rodents. The second step is an extrapolation with large safety factors and the most pessimistic models from high dose to very low dose, or from high concentration to very low concentration, using a linear dose-effect relation. Recently this process, in particular the linear dose-effect, has been severely criticised.^{2,4,5}

The non-threshold linear relation model is based on the theoretical considerations of the stochastic theory, but it has never been validated by data in the very low dose range, and may seriously overestimate the actual effects. During the past years several articles have been published challenging the concept of linear dose-effect relation and advancing arguments for and against.

Shape of the dose-effect relation

The main argument against linearity is that, since

1914, the incidence of cancer at constant age has not increased in industrialised countries despite huge amounts of thousands of new chemicals in our environment. Each year several million tonnes of pesticides, fertilisers, fibres, and plastics are synthesised. These chemical substances did not exist before the second world war and are now produced in massive amounts, but no increase in the incidence of cancer has been reported in populations aged 35 to 70 in the industrialised world. Let us for example consider the stomach and the lung, the two organs most exposed to pollution. The incidence of stomach cancer has diminished considerably in all industrialised countries despite food pollution by fertilisers and pesticides. The incidence of lung cancer in non-smokers has remained constant despite air pollution.

In summary, despite a level of pollution that is far from negligible, the impact of pollution on incidence of cancer is small in industrialised countries. In their authoritative review, Doll and Peto⁶ estimated that less than 2% of cancers are due to air, water, and food pollution, in agreement with several other papers.^{4,5} Some data, however, suggest that the much higher pollution in eastern European countries or in developing countries might increase incidence of cancer.

Another argument against linear extrapolation was recently developed by Ames and Gold^{7,8} who state that plants contain natural pesticides, many of which are carcinogens, as a defence against predators and parasites. Natural carcinogens are present in nearly all vegetables and fruits—for example, apples, bananas, carrots, celery, coffee, lettuce, potatoes, tomatoes, cabbages, and many others. Ames and Gold estimate that we absorb about 10 000 times more pesticides from natural plants than synthetic pesticides originating from pollution. Nevertheless, several reliable surveys carried out in Japan, the United States, Canada, and Europe, have shown that consumption of fruits and vegetables decreases the incidence of cancer. One of the main recommendations of the European code against cancer is to eat fresh fruit and vegetables twice daily.

A third argument against linearity is that a high dose of a toxic substance causes cell death and thereby a compensatory increase of cell proliferation.⁹ Due to the occurrence of errors during DNA synthesis and mitosis, rapidly dividing cells can mutate. Moreover after exposure to a physical or chemical agent that causes DNA damage, DNA repair mechanisms are most effective when cells do not divide. DNA repair is impaired or arrested during DNA duplication and cell mitosis. During these stages of the cell cycle the lesions are fixed and become irreversible. The amount of irreversible lesions, both *in vitro* and *in vivo*, is much smaller when cells remain quiescent. Therefore any agent causing chronic mitogenesis can be indirectly

mutagenic only because it increases the probability of converting DNA damage into mutations.

Arguments in favour of linear models and classical assessment of risks at low doses.^{10 11}

Several arguments favour conservative models. Cell proliferation and organ toxicity are not major determinants in the induction of cancer. Proliferation without carcinogenesis is found in many experimental settings; moreover, even if carcinogenesis is seldom seen without proliferation, it can occur in quiescent tissues. Thus low doses of some agents might be carcinogenic.

By contrast with the thesis of Ames and Gold,^{7 8} bioassays of putative carcinogens might be, at least for some toxic substances, good qualitative predictors of human cancer response, this has been shown in several monographs from the International Agencies for Research on Cancer in Lyon. Linear extrapolation may even in some cases underestimate the lifetime cancer risk.

Finally, as human beings are exposed to a large variety of carcinogens there are possibilities of synergistic interactions; we cannot overlook the possible carcinogenic effect of low doses of toxic agents, and direct investigation is necessary.

The main theme of this debate is the shape of the dose-carcinogenic effect relation at low doses, which is not well known; in pertinent publications I have found few data. One publication¹² is related to tobacco, the carcinogen most studied in humans. In this relation there is a constant a , dose squared and time to the fourth. (Dose is the number of cigarettes smoked a day and the time is in years ($F = a d^2 t^4$).) This relation seems to fit the data well for more than two or three cigarettes a day but we do not know whether it remains valid for low exposure—for example, one cigarette a day or one cigarette every two days.

The example of ionising radiations

Another relation that has been investigated in several studies^{1 4 5} concerns ionising radiation. A linear quadratic relation ($F = a D + b D^2$) has been adopted by the International Commission of Radiological Protection in its report published early this year. This report was criticised by several groups: some radiobiologists would prefer only a squared component and claim that the linear component is not based on good solid data. Others believe that a linear relation would fit the human data adequately in the dose range for which epidemiological data are available. As neither theoretical considerations nor experimental data can assist in choosing the proper function for extrapolating from the available data at relatively high doses to the dose range that is relevant for radioprotection (1 to 5 mSv a year) the best way to progress would be to obtain human data in this dose range.

A possible way to investigate the effects of low dose irradiation is to study the incidence of cancer in relation to the natural radiation to which humans are exposed but which varies according to the characteristics of the soil. In industrialised countries natural irradiation accounts for 82% of the total amount of irradiation that the population receives.^{1 13-15}

As the dose due to natural irradiation varies from 1.5 to 10 mSv, the impact of the variations on incidence of cancer should be detectable if a significant proportion of all cancers were due to ionising radiations.

Radon in particular accounts for 55% of the total irradiation to which we are exposed. Moreover, the radon concentration in air, indoors or outdoors, varies by a factor of more than 10. For example, in France the radon dose received is 20 times higher in the Massif Central than in the Paris region. The same variations are seen in the United Kingdom, United States, or Canada. Doll estimated in 1986 that roughly 1250 cancer deaths are attributable to ionising radiations each year in the United Kingdom, of which 1225 are due to natural irradiation and 25 to man made irradiation. The contribution of man made radiation is small because people are exposed to it mostly when they are adults whereas they are exposed to natural irradiation from birth. If these estimations are valid the variations in the incidence of cancer due to variations in the dose of natural irradiation should be detectable.

A report from the National Radiological Protection Board (NRPB) in 1990 estimated, on the basis of evidence from uranium mines and on the assumption of a linear no threshold dose response, that 5% of all lung cancers in the United Kingdom (1750 cases a year) are due to exposure to indoor radon. In this report the action level was defined at 200 Bq/m³. Awarding grants where radon concentration exceeds this level was proposed. The British Government has agreed to act on the NRPB's advice to reduce unduly high radon levels in about 160 000 homes. The cost is about 210 million pounds sterling. The expected benefit is the prevention of about 140 deaths—that is, about one tenth of the number of cases of lung cancer estimated to be caused by radon. The validity of this estimation is open to discussion, however, as it is based on the debatable assumption of a linear no threshold relation. Bowie and Bowie¹³ expressed serious reservations regarding the conclusions of the NRPB. The main criticisms were, firstly, there is no evidence that in non-smokers lung cancer is caused by exposure to low doses of radon. The Colorado plateau study followed up a cohort of non-smoking miners. There were no cases of lung cancer with cumulative exposure of less than 465 working level months (WLM). At 200 Bq/m³ a person will receive the exposure equivalent to 1 WLM each year. Another criticism of the estimations of the NRPB is that the interaction between low doses of radiation

and smoking remains debatable as the multiplicative model adopted by the NRPB is controversial.

The uncertainties surrounding the linear dose-response model at low doses of radon such as those found in homes will remain until there is direct evidence linking lung cancer with low exposure to radon. Several surveys did not find conclusive evidence and some even reported a negative association between mean radon in dwellings and lung cancer standardised mortality ratios when regional smoking, diet, and social class are accounted for. Case-control studies gave equivocal findings.

Furthermore, it was stated, again by Bowie,¹³ that extrapolation from mines to homes is highly debatable. The characteristics of the air are different and there are pollutants in mines that are not present in air indoors.

Radon research offers an ideal opportunity to investigate the effects of a low dose exposure. The radiation levels found in homes provide sufficient variation at low doses to confirm or refute the linear no threshold dose-response of radiation induced cancer; meanwhile it was considered that the indirect evidence linking low levels of radon and lung cancer is not sufficient to warrant the remedial action proposed in the United Kingdom.

A recent report of the US National Academy of Science¹⁴ concluded that for radium in bones the existence of a threshold is highly probable: "the appearance time increases with decreasing dose and dose rate and characterises a practical threshold of about 0.8 Gy average skeletal dose below which the chance of developing bone cancer from radium-226 and radium-228 during the normal lifetime is extremely small and possibly zero." Hence in this report from a highly respected society, the hypothesis of a threshold is considered most likely.

Hepatoma, another type of human cancer, can be due to exposure to thorotrast, a contrast medium that was widely used from 1930 to 1940. The relation between dose rate and induction of cancer was studied, there also it was found that the delay increased with decreasing doses.

Similarly in the classical paper published early this century, dose and delay were strongly correlated for bladder cancer in a group of 78 workers exposed to 2-naphthylamine. After high dose exposure nearly all the workers in the cohort developed cancer of the bladder and the comparatively short delay was about 12 years. For a median exposure the delay was longer and for a low exposure the delay was so long that the maximum incidence was very low, as after 30 years of follow up all the workers in the cohort were dead from other causes without developing cancer of the bladder. This long delay might help to explain why, when the exposure is low, cumulated incidence remains small.

These data are consistent with experimental

studies in which dogs received various amounts of radioactive isotopes. In these, as in radium painters, for low dose there was no increase in the incidence of osteosarcoma whereas there was a pronounced and early increase in the incidence after relatively high doses. In these experiments the dose-effect relation was certainly non-linear. Another point that deserves discussion is the influence of dose rate. This topic has been investigated in many experiments carried out with ionising radiation.¹⁵ For example, the incidence of thymic lymphoma in mice was studied after irradiation. For a given dose, for instance 1 Gray, there was practically no increase at low dose rate and a considerable increase at high dose rate. Dose rate is equivalent to concentration and these data show that it cannot be neglected, probably because the probability of repair is influenced by the dose rate or the concentration.

Conclusion

The goals for the future, at least in studies with ionising radiations, are to answer a few crucial questions. The first is: is it valid to extrapolate from high or median doses to very low doses? and what is the reliability of this extrapolation? This reliability should be discussed when estimating the risk by extrapolation. For example, could we extrapolate from the incidence of liver cancer that is found among people who drink a litre of wine per day, which means 30 litres of alcohol per year, to somebody who, once every two years eats a plum cake flavoured with alcohol: that is a dose of about 10^{-4} less. A range of four to five orders of magnitude is typically one that is relevant in protection against carcinogens. Another question is related to threshold.⁴ Is there a practical threshold if the delay between exposure and cancer emergence increases when the dose decreases, or is it an actual threshold if there is full DNA repair at low dose rate exposure?

Unfortunately, experimental data cannot yet give us the answers that are needed. The only way to get them is to produce direct human data. There are two possible ways to progress. The first is to carry out huge surveys, for example to assess incidence of cancer in regions with a high or low natural irradiation, on the basis of cancer registries. This type of research has not yet been done on a sufficiently large scale. Cancer registries could be useful and efficient tools and we should exploit their data much more than in the past, unfortunately this method can be used only for agents to which all the population is exposed, for example water or air pollution or natural ionising radiation.

A second tool is meta-analyses of data reported in several surveys. Meta-analyses are, however, exposed to a bias, which is the privileged publication of positive results. This is true in both epidemiology and therapeutic cancer research. Most scientists

publish papers only when they find a positive result; whereas they do not publish papers when the study is negative, or the papers are not accepted in journals with a large audience. This bias has to be overcome to be able to carry out reliable meta-analysis.

Finally if direct human data are required, we should simultaneously do everything that we can to deepen our understanding of the shape of the dose effect relation in the low dose region. As stated by Cohen and Ellwein⁹ in *Science*, "as the mechanisms of carcinogenesis become more thoroughly understood, a more rational approach can be taken for extrapolation from high dose experimental data in animals to low dose natural exposure and assessment of the risk faced by the human populations exposed to chemical agents." Hence fundamental and epidemiological researchers should cooperate closely.

The two possible approaches, either large surveys or a better analysis of the mechanisms of carcinogenesis for the agents that have to be considered in protection are not mutually exclusive; in fact, they are complementary.

Requests for reprints to: Professor M Tubiana, Institut Gustave Roussy, 39 rue Camille Desmoulins, 94800 Villejuif, France.

M TUBIANA

*French National Academy of Science,
Paris, France*

- 1 UNSCEAR 1988. *Sources effects and risks of ionizing radiation*. United Nations, NY: Report to the General Assembly, with annexes. 1988, pp647.
- 2 Tubiana M, Lafuma J, Masse R, Latarjet R. The assessment of the carcinogenic effect of low dose radiation. In: Gerber GB *et al*, eds. *The future of human radiation research*. *British Institute Radiation Report* 1991;22:109–19.
- 3 Abelson PA. Testing for carcinogens with rodents. *Science* 1990;249:358.
- 4 Académie des Sciences. *Risques de rayonnements ionisants et normes de radioprotection*. Paris, France: Académie des Sciences 1989, pp72 (Rapport 23).
- 5 Latarjet R, Tubiana M. The risks of induced carcinogenesis after irradiation at small doses. The uncertainties which remain after the 1988 UNSCEAR report. *Int J Radiat Oncol Biol Phys* 1989;17:237–40.
- 6 Doll R, Peto R. The causes of cancer—Quantitative estimates of avoidable risks of cancer in the United States today. *J Natl Cancer Inst* 1981;66:1191–308.
- 7 Ames B, Gold LS. Too many rodent carcinogens: mitogenesis increases mutagenesis. *Science* 1990;249:970–1.
- 8 Ames B, Gold LS. Chemical carcinogenesis: too many rodent carcinogens. *Proc Natl Acad Sci USA* 1990;87:7772–6.
- 9 Cohen SM, Ellwein LB. Cell proliferation in carcinogenesis. *Science* 1990;249:503–4.
- 10 Weinstein IB. Mitogenesis is only one factor in carcinogenesis. *Science* 1991;251:387–8.
- 11 Infante PF. Prevention versus chemophobia: a defence of rodent carcinogenicity tests. *Lancet* 1991;337:538–40.
- 12 Muir CS. Epidemiology, basic science and the prevention of cancer. Implications for the future. *Cancer Res* 1990;50:6441–8.
- 13 Bowie C, Bowie SHV. Radon and health. *Lancet* 1991;337:409–13.
- 14 Committee on the biological effects of ionizing radiations. *BEIR IV Health risk of radon and other internally deposited alpha-emitters*. Washington DC: National research Council. National Academy of Sciences, 1988, pp602.
- 15 Tubiana M, Dutreix J, Wambersie A, Bewley DK. *Introduction to radiobiology*. London, UK: Taylor and Francis. 1990, pp 371.